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The Brief Case: A Rare Case of Invasive Amebiasis Requiring Emergency Subtotal Colectomy in an HIV-Positive Man

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CASE

In April 2017, a 56-year-old HIV-positive man was transferred from another institution to our regional infectious disease unit having presented with 2 weeks of profuse, watery diarrhea accompanied by intermittent, fresh bleeding of the rectum. Symptoms had started during a 2-month vacation to Indonesia, Vietnam, and Malaysia. While on vacation, he stayed in hotels in urban areas, had no rural travel, and drank only bottled water. He reported that he was not a man who has sex with men (MSM) and preferred to discuss his further sexual history confidentially with the genitourinary medicine team. Two months prior to admission, his CD4 count was 194 cells/mm^3, and while taking an antiretroviral therapy regimen consisting of tenofovir, emtricitabine, and nevirapine, his HIV RNA had been undetectable in his plasma for 3 years.

Initial investigations showed a raised C-reactive protein (CRP) level (282 mg/liter; normal, $<$5 mg/liter), neutrophilia (12.9 $\times$ 10^9/liter; normal, 2.0 to 7.5 $\times$ 10^9/liter), a prolonged prothrombin time (19.8 s; normal, 9 to 13 s), and a mild transaminitis (alanine aminotransferase, 55 U/liter; normal, $<$35 U/liter). Oral azithromycin was started for presumed infective gastroenteritis, and intravenous (i.v.) fluid resuscitation was given. Routine fecal microscopy and cultures identified no bacteria, ova, cysts, or parasites, and three routine blood cultures were negative.

Two days after transfer to our unit, the patient developed abdominal distension, generalized peritonitis, and tachycardia, and his CRP level rose to 395 mg/liter. An urgent contrast-enhanced computed tomography (CT) scan of his abdomen showed severe pancolitis, with perforations of the cecum and sigmoid colon, and two small low-density lesions in the liver. He was prescribed i.v. ceftriaxone and metronidazole and underwent an emergency laparotomy. This revealed a gangrenous necrotic cecum with gross disruption of its anterior wall and four-quadrant fecal contamination of the peritoneal cavity. Serosal evidence of colitis was found throughout the colon but diminished distally and spared the rectum. The colon was resected in a standard manner, the distal sigmoid was transected, and the remaining rectal stump was sutured to the anterior wall of the peritoneal cavity. A 10-liter peritoneal lavage was performed, and a spouting end ileostomy was formed in the right iliac fossa.

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For answers to the self-assessment questions and take-home points, see https://doi.org/10.1128/JCM.01704-17 in this issue.

Lactobacillus rhamnosus and *Streptococcus anginosus* were isolated from intra-abdominal drains, *Enterococcus gallinarum* and *Escherichia coli* were identified in surgical wound swabs, and the patient continued on i.v. ceftriaxone and metronidazole. Two weeks into his hospital stay, the patient developed cholestatic derangement of liver function tests, with gamma-glutamyl transferase and alkaline phosphatase reaching peaks of 2,946 U/liter (normal, 11 to 50 U/liter) and 2,046 U/liter (normal, 30 to 200 U/liter), respectively. A further liver CT scan showed no change in the lesions, which radiologists reported as more likely to represent hemangiomas than amebic or pyogenic abscesses. Ceftriaxone was discontinued, which resulted in normalization of liver function tests. Antimicrobial therapy was switched to tigecycline to complete treatment of the patient's resolving intra-abdominal sepsis while avoiding further derangement of liver function tests.

The subtotal colectomy specimen was received by the histopathology department, with a perforated necrotic cecum and associated fibrinous exudate found on the serosa. Upon opening the specimen, there were multiple, discrete, undermining ulcers with hyperemic edges throughout the proximal and transverse colon, but the distal colon and the terminal ileum were spared. The ulcers were of various sizes (1.5 to 2.0 cm), were orientated transversely across the colon, and had necrotic yellow debris covering the ulcer base (Fig. 1). The intervening mucosa was macroscopically normal. On microscopy, there were foci of superficial erosion of the colonic mucosa, undermining ulceration into the submucosa (Fig. 2A), and transmural ulceration and necrosis, including at the site of the perforation in the cecum (Fig. 2B). Within the ulcers, there was abundant necrotic amorphous debris containing nuclear debris and the trophozoites of amebae ($\leq$30 μm in size), some with ingested erythrocytes, but only scanty neutrophils (Fig. 2C and D and inset). No amebic cysts were seen. The colon between the ulcers was normal.

Amebic serology was strongly positive (titer, 1:512), and an ameba latex test of a serum sample was positive. Amebiasis was treated for a total of 14 days with i.v. metronidazole. This was followed by 7 days of oral paromomycin for luminal clearance.

Postoperatively, the patient had a prolonged ileus and required total parenteral nutrition. Complications included a superficial dehiscence of the abdominal wound and a coagulopathy requiring correction. He was discharged after 5 weeks in the hospital and completed 6 weeks of tigecycline therapy as an outpatient.

He was seen in our clinic in May 2018 and had gained 16 kg in weight. He was eating a normal diet and able to use his stoma independently, and his surgical wound dehiscence had healed well. The patient has been scheduled for an ileorectal anastomosis procedure to restore bowel continuity. This will be followed by a further week of

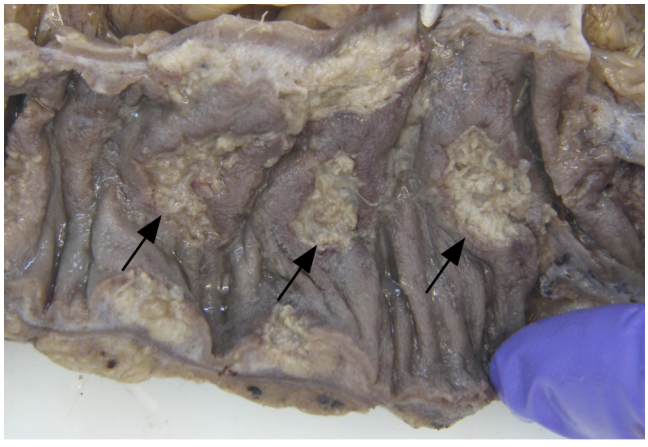

FIG 1 Discrete ulcers (1.5 to 2.0 cm in size) with hyperemic edges and containing necrotic yellow debris lie transversely within the colon. Arrows indicate the ulcers.

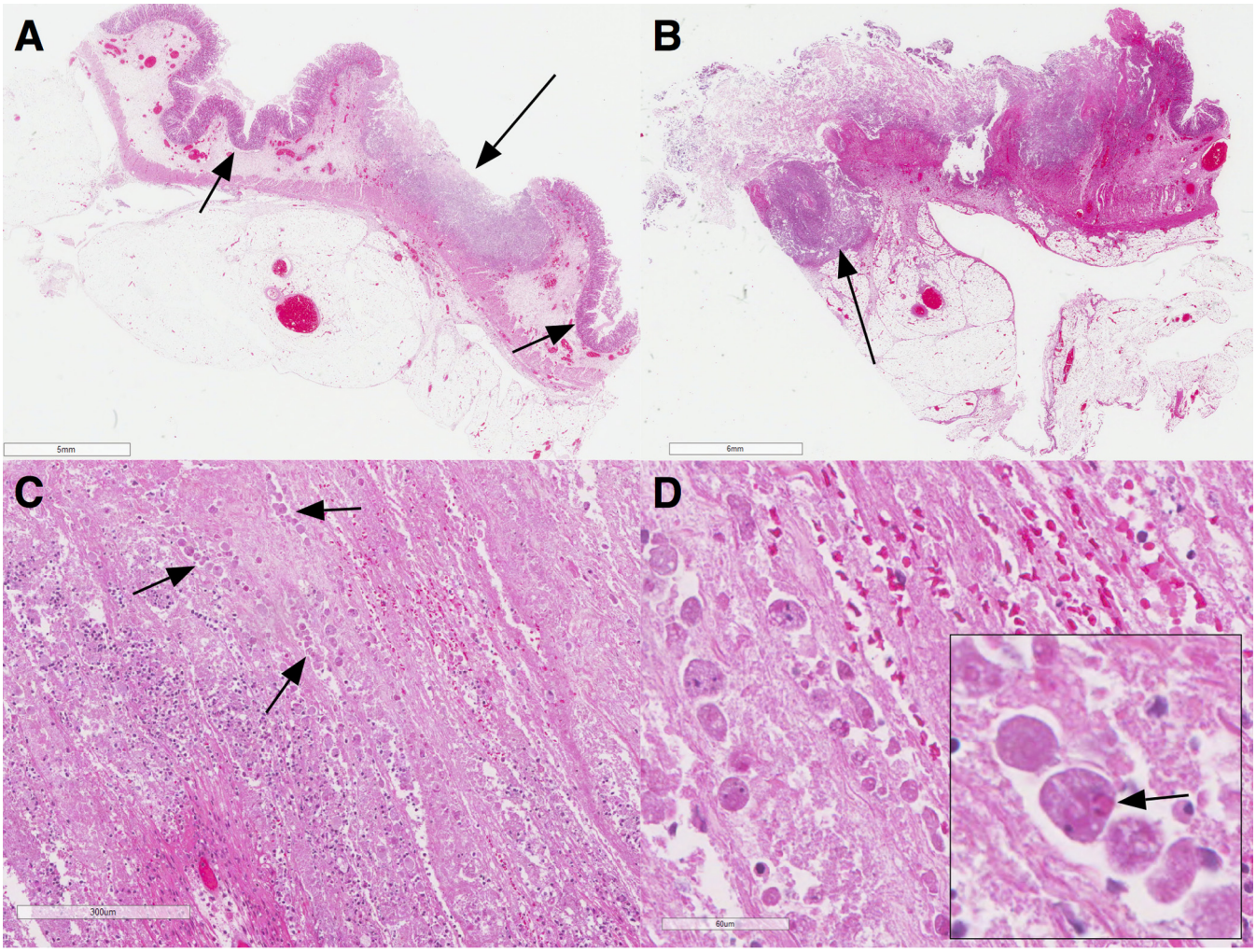

FIG 2 (A) A discrete undermining (flask-shaped) ulcer is separated by normal colon as observed with hematoxylin and eosin (H&E) staining. The long arrow indicates the undermining ulcer, and short arrows indicate the normal colon. (B) Transmural ulceration and necrosis at the edge of the cecal perforation, indicated by the long arrow (H&E staining). (C) Abundant amebae are seen in the amorphous eosinophilic necrotic material within the ulcers (H&E staining). (D) Trophozoites have distinct cell membranes, abundant foamy cytoplasm, and an eccentric nucleus (inset, arrow) with peripheral chromatin margination and a central karyosome (H&E staining).

oral paromomycin to eliminate any residual luminal *Entamoeba histolytica* organisms in the remaining rectum.

DISCUSSION

Amebiasis is caused by *Entamoeba histolytica*, a protozoon commonly found in low-resource settings, including Africa, India, Mexico, and parts of central/south America and Southeast Asia. The predominant risk factors for amebiasis include travel to or residence in areas of endemicity, low socioeconomic status, being a man who has sex with men (MSM), being institutionalized, extremes of age (young/old), pregnancy, iatrogenic immunosuppression (including corticosteroids), alcoholism, malignancy, and malnutrition (1). Amebic cysts are transmitted feco-orally (including during sexual contact) (2), and the majority of infections are asymptomatic (1). However, in the small intestine, cysts can develop into trophozoites. Trophozoites then penetrate the large bowel mucosa, causing invasive disease, including dysentery, amebic liver abscesses (ALA), and other extraintestinal manifestations.

Intestinal amebiasis presents 1 to 3 weeks following infection with symptoms, including fever, abdominal pain, and bloody diarrhea. Fulminant amebic colitis with or without toxic megacolon occurs rarely (1 in 200) but has a mortality of up to 40% (1).

Extraintestinal manifestations of invasive amebiasis include ALA, brain abscesses, and pleuropulmonary, cardiac, or cutaneous involvement. ALA are the most common extraintestinal manifestation, occurring a median of 12 weeks following exposure (although the lag period can be years). Symptoms of ALA include fever and upper right quadrant pain, but jaundice is uncommon. Of note, less than one-third of patients with ALA report concurrent diarrhea, but clinical history may reveal an episode of dysentery in preceding months (1). Radiological imaging with CT or ultrasound may be characteristic of ALA, with the majority of abscesses being solitary subcapsular lesions found in the posterior part of the right lobe (3). However, imaging of the abdomen does not differentiate colitis or perforation caused by invasive amebiasis from colitis or perforation of other etiology (3).

The evidence supporting a diagnosis of amebiasis in this patient was 2-fold, with positive serology and pathology. The latex agglutination test is a rapid screening test for circulating amebic antibody, which is performed on serum prior to the more sensitive indirect fluorescent assay (IFA). The IFA titer in a serum sample taken 10 days into the illness was 1:512. Titers of greater than 1:256 are strongly suggestive of invasive amebiasis, according to our local laboratory thresholds. The macroscopic and microscopic appearances (described above) in the resection specimen were classical for amebic colitis. Other serological assays are available to support the diagnosis of amebiasis; enzyme-linked immunosorbent assay (ELISA) is the most commonly used assay in clinical laboratories, predominantly because the IFA is more technically challenging to perform (4). Nevertheless, an IFA offers several advantages over an ELISA. First, the IFA has higher sensitivity (93.6%) and specificity (96.7%). Second, IFA titers drop 8 to 12 months posttherapy, whereas ELISA titers do not. This change in IFA titers, coupled with serial measurement of IFA IgM levels, can be used to differentiate between previous and current amebiasis and also to monitor response to treatment (4, 5). It should be noted that, despite our patient having severe invasive amebiasis with a high burden of organisms in the colon, fecal microscopy was negative. Fecal microscopy is less reliable than the serological tests mentioned above because its sensitivity is 33 to 50%. False-positive results can occur due to misidentification of macrophages as trophozoites or of polymorphonuclear cells as cysts or due to the presence of other *Entamoeba* species (e.g., the morphologically identical but nonpathogenic *Entamoeba dispar*). In settings in which diagnostic tests for amebiasis are limited to microscopy, the detection rate can be increased to 85% by examining 3 fresh fecal samples over a 10-day period (1, 3, 4).

The aims of treatment of amebiasis are to eliminate invasive trophozoites and to eradicate carriage of *E. histolytica* cysts in the intestine. The main treatment options include metronidazole (500 to 750 mg three times a day orally for 10 days) or tinidazole (2 g once daily for 3 days) for invasive disease. A systematic review suggested that tinidazole had a reduced clinical failure rate and few side effects compared with metronidazole (6). While metronidazole or tinidazole alone may eradicate intestinal cyst carriage, a second luminal agent, such as paromomycin (25 to 30 mg per kg of body weight per day for 7 days) or diloxanide furoate (500 mg three times a days for 10 days), is still recommended (6).

There are a number of important points to note from this case. Our patient had been in an area where amebae are endemic for a relatively short period of 2 months, staying in good-quality accommodations. This is in line with evidence of an acknowledged risk of amebiasis with even short periods of travel; one case series found that 35% of travelers with ALA had spent less than 6 weeks in an area of endemicity (7). Being male has also been recognized as a risk factor for ALA (7 to 10 times higher incidence) but not amebic dysentery (8). Iatrogenic immunosuppression is a risk factor for severe amebiasis (1), but an association with HIV-related immunosuppression is less clear; our patient had well-controlled HIV disease on antiretroviral therapy without any WHO grade 3 or 4 complications, but his CD4 count before this illness was only 194 cells/mm^3, indicating the possibility of incomplete immune reconstitution.

Evidence of an association between amebiasis and HIV relates predominantly to

ALA. A study in Japan showed that a high anti-*E. histolytica* antibody titer in newly registered HIV patients was an independent predictor of developing invasive amebiasis (9). Studies in Taiwan and Hong Kong suggest an increase in the prevalence of invasive amebiasis in HIV-positive men, but this is potentially confounded by oro-anal sexual contact (10, 11). One report from the United States found that, of patients with ALA who had not visited areas of endemicity, 38% were HIV positive (12), and a further case series found no difference in clinical and radiological presentation of patients with ALA who were HIV positive or HIV negative (13). Overall, MSM may be at increased risk of amebiasis, and clinicians should have a lower threshold of suspicion for the diagnosis in relevant returning travelers, even those who have a short travel duration.

Luminal amebicidal treatment is recommended to eradicate colonic carriage and prevent recurrence. However, we were faced with the conundrum of whether this was necessary in this case, as the colon had been largely removed. On the presumption that there was a high organism burden, given the severe disease, we gave paromomycin in the immediate postoperative period. Oral preparations of paromomycin were expected to reach only the small bowel and be cleared into the stoma; therefore, the rectal stump remained untreated. As no rectal preparations are available, we decided to re-treat our patient with paromomycin following the restoration of bowel continuity.

This rare case of invasive amebiasis requiring subtotal colectomy in an HIV-positive man highlights a number of important learning points. First, invasive amebiasis should be considered in returning travelers with diarrhea, even when duration of time spent in an area of endemicity has been limited. Second, although MSM may be at greater risk of amebiasis, there is no convincing evidence to suggest that having HIV disease *per se* increases the propensity to, or severity of, amebic disease. Finally, no rectal preparations of luminal agents are currently available, so once bowel continuity is restored in this patient, we will commence a second course of luminal treatment to eliminate any remaining amebae in the untreated rectum.

SELF-ASSESSMENT QUESTIONS

1. Which of the following is a proven risk factor for invasive amebiasis?
    A. Being female
    B. HIV infection
    C. Inflammatory bowel disease
    D. Prolonged antibiotic use
    E. Travel to or residence in an area of endemicity
2. What is the most commonly used serological assay in the diagnosis of amebiasis?
    A. Complement fixation
    B. ELISA (enzyme-linked immunosorbent assay)
    C. IFA (indirect fluorescent assay)
    D. Immunochromatographic lateral-flow assay
    E. Latex agglutination
3. Which of the following is an appropriate treatment regimen for invasive amebiasis?
    A. Ceftriaxone and metronidazole
    B. Metronidazole or tinidazole
    C. Paromomycin or diloxanide furoate
    D. Metronidazole or tinidazole and paromomycin or diloxanide furoate
    E. Co-trimoxazole

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